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Perkins Coie LLP
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EXAMINER	
SHEN, WU CHENG WINSTON	

ART UNIT	PAPER NUMBER
1632	

NOTIFICATION DATE	DELIVERY MODE
10/13/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentprocurement@perkinscoie.com

Advisory Action Before the Filing of an Appeal Brief	Application No.	Applicant(s)	
	10/541,354	BULLERDIEK, JORN	
	Examiner	**Art Unit**	
	WU-CHENG Winston SHEN	1632	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 01 October 2010 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires *6* months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.
   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.
   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *92-94,100 and 101*.
   Claim(s) withdrawn from consideration: *95-99*.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.
12. ☐ Note the attached Information *Disclosure Statement*(s). (PTO/SB/08) Paper No(s). _____
13. ☐ Other: _____.

/Wu-Cheng Winston Shen/
Primary Examiner, Art Unit 1632

Continuation of 11. does NOT place the application in condition for allowance because:

(I) Applicant argues that Andersson alone or in combination with Okamoto and Kirkpatrick do not destroy unity of invention. Applicant states that Andersson et al. are totally silent about the use of HMGB1 as a drug and about the role of HMGB1 in promoting angiogenesis. Moreover, to the contrary there is a teaching away from combining Andersson et al. with the other cited documents of the prior art. Applicant states that, accordingly, the feature "methods for promoting angiogenesis comprising incubating a tissue with an HMGB1 protein" is not shown in the prior art and thus can be a special technical feature under PCT Rule 13.2. Applicant states that, in the light of the foregoing, the feature "methods for promoting angiogenesis comprising incubating a tissue with an HMGB1 protein" is a special technical feature which links the inventions of claim 92 and claim 99. Thus, claim 92 and claim 99 relate to a single general inventive concept under PCT Rule 13.1 and do not lack unity of invention.

In response, Applicant's arguments have been fully considered and found mot persuasive.
As documented on pages 2-4 of the Final office action mailed on 04/01/2010, in the Restriction mailed on 07/16/2009, claim 99 is directed to the method according to claim 92, further comprising incubating said tissue or fragment thereof with a translation product derived from the VEGF gene or a fragment thereof. The translation product derived from the VEGF gene or a fragment thereof recited in claim 99 is not encompassed by elected Group II invention. Therefore, claim 99 had been assigned to a new group, Group XXVII (the Restriction requirement mailed on 06/18/2008 listed Group I-XXVI). The inventions recited in claim 92 and claim 99 do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: Applicant's claims encompass multiple inventions with multiple methods (methods of promoting angiogenesis requires HMGB1 protein, and methods of promoting angiogenesis requires both HMGB1 and VEGF protein), and do not have a special technical feature which link the inventions one to the other, and lack unity of invention. The common technical feature is methods of promoting angiogenesis comprising incubating a tissue with an HMGB1 protein. However, this common technical feature cannot be a special technical feature under PCT Rule 13.2 because the feature is shown in the prior art (See 103 rejection in this office action). The search for claim 99 of Group XXVII and the search for claim 92 of Group II is distinct one from each other and not co-extensive and thereby presents search burdens on the examiner. However, it is further noted, that search burden is not germane to PCT lack of unity practice.

With regard to election of species, translation product HMGB1, translation product HMGB2, and translation product HMGB3 recited in claim 93 are different HMGB proteins belonging to HMGB family with distinct amino acid sequences, and different in structures and functions. Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 CFR 1.141. If claims are added after the election, applicant must indicate which are readable upon the elected species. MPEP § 809.02(a). As Applicant elected HMGB1 as elected species of the limitation "a translation product of a high mobility growth protein gene, or a fragment thereof" recited in claim 92, claim 95 reciting various HMGA proteins and claim 97 reciting "wherein one translation product is selected from the HMGA family" are directed on non-elected species. Claim 96 depends from claim 95, and claim 98 depends from claim 97.

Therefore, as discussed in two preceding paragraphs, claims 95-99 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim.
Claims 92-101 are pending. Claims 92-94, 100, and 101 are currently under examination to the extent of elected species HMGB1 as "a translation product of a high mobility growth protein gene".

The requirement is still deemed proper and is therefore made FINAL.

It is noted that claims 92-94, 100, and 101 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Andersson et al. (Andersson et al., HMGB1 as a DNA-binding cytokine, J Leukoc Biol. 72(6):1084-91, 2002) in view of Okamoto et al. (Okamoto et al., Angiogenesis induced by advanced glycation end products and its prevention by cerivastatin, FASEB J. 16(14):1928-30, 2002), and Kirkpatrick et al. (Kirkpatrick et al., Tissue response and biomaterial integration: the efficacy of in vitro methods, Biomol Eng. 19(2-6):211-7, 2002). More detailed discussions in this regard are provided below.

(II) Applicant's arguments have failed to overcome the rejection of claims 92-94, 100, and 101 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Andersson et al. (Andersson et al., HMGB1 as a DNA-binding cytokine, J Leukoc Biol. 72(6):1084-91, 2002) in view of Okamoto et al. (Okamoto et al., Angiogenesis induced by advanced glycation end products and its prevention by cerivastatin, FASEB J. 16(14):1928-30, 2002), and Kirkpatrick et al. (Kirkpatrick et al., Tissue response and biomaterial integration: the efficacy of in vitro methods, Biomol Eng. 19(2-6):211-7, 2002). Applicant's arguments filed 10/01/2010 have been fully considered and they are not persuasive. Previous rejection is maintained for the reasons of record advanced on pages 7-13 of the office action mailed on 10/01/2010.

Applicant argues that a skilled artisan would understand that Andersson teaches HMGB1 is a potent pro-inflammatory cytokine that acts as a strong mediator of macrophage activation (Andersson et al., p. 1085, right column, 2nd complete paragraph). Stimulated macrophages actively secrete HMGB1 to promote inflammation and in turn, stimulate production of multiple, proinflammatory cytokines (abstract). Applicant states that the Office Action points to nothing in Okamoto to indicate that the angiogenesis effects observed in vitro with glycer-AGE or glycol-AGE would occur in vivo where Andersson makes clear that a pro-inflammatory environment is promoted by HMGB1. In addition, the Office Action appears to presume only a single and common pathway for HMGB1 and glycer-AGE or glycol-AGE exists. Under the circumstances, the suggestion that the results observed by Okamoto in vitro would be observed in vivo is nothing more than a conclusory statement that lacks a rational underpinning. Moreover, it cannot even be concluded that by combining the references a predictable result would be obtained. For at least those reasons, a prima facie case capable of supporting a legal conclusion of obviousness has not been set forth.

Applicant further argues that Andersson teaches away from the use of HMGB1 in methods of promoting angiogenesis in a tissue, and from combining Andersson with a reference that might suggest such a use. HMGB 1 is a potent pro-inflammatory cytokine that acts

as a strong mediator of macrophage activation (Andersson et al., p. 1085, right column, 2nd complete paragraph). Stimulated macrophages actively secrete HMGB 1 to promote inflammation, and in turn, stimulate production of multiple proinflammatory cytokines (abstract). Andersson et al. conclude that HMGB1 is a potent therapeutic target rather than considering HMGB 1 as a drug which can be taken/administered (see page 1089, right column, which describes the "opportunity" to successfully treat experimental sepsis by late administration of neutralizing HMGB 1 antibodies). That Andersson views HMGB1 as a therapeutic target is also emphasized by the teachings of the paragraph under the title "Lung inflammation" on page 1089, right column (Andersson et al.). From that discussion in Andersson, a skilled artisan would understand that a) administration of HMGB1 leads to cytokine production, b) HMGB1, subsequently, mediates acute inflammatory lung injury and c) HMGB 1 is a target for anti-HMGB1 antibodies.

Applicant states that in light of the foregoing, Applicant further submits that a person skilled in the art would have seen no cause to use HMGB1 as a drug. This holds true although Okamoto et al. teach that AGE proteins elicit changes associated with angiogenesis and Andersson et al. teach that HMGB1 is a ligand for RAGE binding. Taking Andersson et al. as a starting point, a person skilled in the art aware of Okamoto et al. would not use HMGB1 as a drug, but would instead search for a drug targeting HMGB1. In deed, Andersson et al. even speculate about the latter as the last paragraph on page 1090 reads as follows: "Will HMGB1 be validated as a clinical target, like TNF or IL-1, to modulate acute or chronic inflammation, or will it be too dangerous to interfere with a molecule that is so central for the interplay between necrotic cell death with subsequent inflammation and repair responses?

In response, claim 92 filed on 06/22/2009 reads as follows: A method of promoting angiogenesis in a tissue or part thereof, comprising incubating a tissue or part therefore with a translation product of a high mobility growth protein gene, or a fragment thereof and, optionally, obtaining or recovering the tissue or an intermediate thereof. It is noted that claim 92 encompasses both in vitro and in vivo aspects of promoting angiogenesis in any tissue or part thereof comprising incubating a tissue or part therefore with a translation product of a high mobility growth protein gene. In fact, dependent claim 100 specifically recited "wherein said tissue is an in vitro culture tissue". In this regard, Okamoto et al. teaches in vitro human adult skin microvascular endothelial cells (EC) cultured in endothelial basal medium. Therefore, the arguments that "the results observed by Okamoto in vitro would be observed in vivo is nothing more than a conclusory statement that lacks a rational underpinning" have been fully considered and found not persuasive.

For the clarity of record, the rejection for the reason of record documented on pages 7-13 of the Final office action mailed on 04/01/2010 are reiterated below.

Andersson et al. teaches that extracellular HMGB1 as a potent macrophage-activating factor, signaling via the receptor for advanced glycation end-products to induce inflammatory responses (See abstract, left column, page 0184, Andersson et al.). Andersson et al. teaches that HMGB1 is a specific and saturable ligand for RAGE binding with a higher affinity than the receptor's other known ligands, advanced glycation end products (AGEs). Andersson et al. teaches that HMGB1-induced intracellular signaling through RAGE can activate two different cascades, one involving the small GTPases Rac and Cdc42, leading to cytoskeletal reorganization, and a second that involves the Ras-mitogen-activated protein (MAP) kinase pathway and subsequent nuclear factor (NF)-kappaB nuclear translocation-mediating inflammation (See left column, page 1087, Andersson et al.). Andersson et al. teaches that there are two distinctly separate ways for HMGB1 to be secreted from a cell: HMGB1 can be passively released from the nuclei of necrotic or disintegrating, damaged cells or actively secreted from activated macrophages/monocytes or pituicytes, which does not involve cell death (See Figure 2, shown below, Andersson et al.).

Andersson et al. does not explicitly teach (i) the effect of HMGB1 protein in promotion of angiogenesis recited in claims 92-94, and (ii) the limitation wherein said tissue or part thereof is an in vitro tissue recited in claim 100, and (iii) the limitation wherein said tissue is an explanted tissue recited in claim 101.

With regard to (i) the effect of HMGB1 protein in promotion of angiogenesis recited in claims 92-94, and (ii) the limitation wherein said tissue or part thereof is an in vitro tissue recited in claim 100, Okamoto et al. teaches that when human skin microvascular endothelial cells (EC) were cultured with glycer-AGE or glycol-AGE, growth and tube formation of EC, the key steps of angiogenesis, were significantly stimulated. The AGE-induced growth stimulation was significantly enhanced in AGE receptor (RAGE)-overexpressed EC. Furthermore, AGE increased transcriptional activity of nuclear factor-kappaB (NF-kappaB) and activator protein-1 (AP-1) and then up-regulated mRNA levels of vascular endothelial growth factor (VEGF) and angiopoietin-2 (Ang-2) in EC. Okamoto et al. teaches that cerivastatin, a hydroxymethyl-glutaryl CoA reductase inhibitor; pyrrolidinedithiocarbamate; or curcumin was found to completely prevent the AGE-induced increase in NFkappaB and AP-1 activity, VEGF mRNA up-regulation, and the resultant increase in DNA synthesis in microvascular EC (See abstract, Okamoto et al., 2002).

With regard to (iii) the limitation wherein said tissue is an explanted tissue recited in claim 101, Kirkpatrick et al. teaches that implantation involves tissue trauma, which evokes an inflammatory response, coupled to a wound healing reaction, involving angiogenesis, fibroblast activation and matrix remodeling. Kirkpatrick et al. teaches that three principal fields of research can yield useful data to understand these phenomena better: studies on explanted biomaterials, animal models and relevant in vitro techniques. Kirkpatrick et al. teaches the application of endothelial cell (EC) culture systems to study the effects, including pro-inflammatory cytokines, chemokines, of implanted tissue, and material (e.g. metal ions, particulate debris) factors on the regulation of the inflammatory and angiogenic response (See abstract, Kirkpatrick et al.).

Therefore, it would have been obvious for one of ordinary skill in the art at the time the claimed invention was made to combine the teachings of Andersson et al. regarding HMGB1 is a specific and saturable ligand for RAGE binding with a higher affinity than the receptor's other known ligands, advanced glycation end products (AGEs); HMGB1-induced intracellular signaling through RAGE can activate two different cascades, one involving the small GTPases Rac and Cdc42, leading to cytoskeletal reorganization, and a second that involves the Ras-mitogen-activated protein (MAP) kinase pathway and subsequent nuclear factor (NF)-kappaB nuclear translocation-mediating inflammation, with the teachings of (i) Okamoto et al. regarding activation of RAGE signaling pathway promotes angiogenesis in cultured human skin microvascular endothelial cells (EC), and the teachings of (ii) Kirkpatrick et al. regarding the application of endothelial cell

(EC) culture systems to study the effects, including pro-inflammatory cytokines, chemokines, of implanted tissue, and material factors, including metal ions, particulate debris, on the regulation of the inflammatory and angiogenic response in an explanted tissue, to arrive at the claimed methods of method of promoting angiogenesis in a tissue as recited in claims 92-94, 100, and 101 of instant application.

One of ordinary skill in the art would have been motivated to combine the teachings of Andersson et al. Okamoto et al. and Kirkpatrick et al. because (i) Andersson et al. teaches HMGB1 is a DNA-binding cytokine and a specific and saturable ligand for RAGE binding, and Andersson et al. proposes further investigation of relationship between vascular endothelial cells (EC), macrophage and HMGB1 (See left column, page 1090, Andersson et al.), (ii) Okamoto et al. teaches activation of RAGE signaling pathway promotes angiogenesis in cultured human skin microvascular endothelial cells (EC); and (iii) Kirkpatrick et al. teaches the application of endothelial cell (EC) culture systems to study the effects, including pro-inflammatory cytokines, chemokines, of implanted tissue and material factors on the regulation of the inflammatory and angiogenic response.

There would have been a reasonable expectation of success given (i) established interaction between HMGB1 and RAGE leading to transcriptional activation of NK-kappaB transcription factors via nuclear translocation mediated by RAGE signaling pathway, by the teachings of Andersson et al., (ii) successful demonstration of activation of RAGE signaling pathway promotes angiogenesis by activation of NK-kappaB transcription factors in cultured human skin microvascular endothelial cells (EC), by the teachings Okamoto et al. (See Figures 1-3), and (iii) successful demonstration of application of endothelial cell (EC) culture systems to study the effects, including pro-inflammatory cytokines, chemokines, of implanted tissue, and material factors on the regulation of the inflammatory and angiogenic response in an explanted tissue, by the teachings of Kirkpatrick et al. (See Figures 2 and 5).

Thus, the claimed invention as a whole was clearly prima facie obvious

The Examiner would like to direct Applicant's attention to recent decision by U.S. Supreme Court in KSR International Co. v. Teleflex, Inc. that forecloses the argument that a specific teaching, suggestion, or motivation is an absolute requirement to support a finding of obviousness. See recent Board decision Ex parte Smith, --USPQ2d--, slip op. at 20, (Bd. Pat. App. & Interf. June 25, 2007) (citing KSR, 82 USPQ2d at 1936) (available at http://www.uspto.gov/web/offices/dcom/bpai/prec/fd071925.pdf). The Examiner notes that in the instant case, even in the absence of recent decision by U.S. Supreme Court in KSR International Co. v. Teleflex, Inc., the suggestion and motivation to combine Andersson et al. Okamoto et al. and Kirkpatrick et al. have been clearly set forth above in this office action.

It is noted that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); In re Merck & Co., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

In response to Applicant's arguments that "Andersson views HMGB 1 as a therapeutic target is also emphasized by the teachings of the paragraph under the title "Lung inflammation" on page 1089, right column (Andersson et al.)", the arguments have been fully considered and found not persuasive.

In this regard, it is worth noting that Andersson et al. provides the following statements at the end of discussions: It is clear that any "neutralizing antibodies" should be screened for inhibition of HMGB1-activated TNF release in macrophages. These basic tools will enable assessment of fundamental questions that still need to be addressed; e.g., What is the quantitative relationship between the extracellular HMGB1 pool from necrotic cells versus active secretion from macrophages, platelets, vascular endothelial cells, and other putative HMGB1 sources? Are there other HMGB1 receptors than RAGE? To what extent are TNF and other proinflammatory molecules needed for the proinflammatory role of HMGB1? Will HMGB1 be validated as a clinical target, like TNF or IL-1, to modulate acute or chronic inflammation, or will it be too dangerous to interfere with a molecule that is so central for the interplay between necrotic cell death with subsequent inflammation and repair responses? These are indeed very exciting questions that need to be addressed and elucidated in the near future (See page 1090, left column, Andersson et al., 2002).

Therefore, the teachings by Andersson et al. are certainly not limited to down-regulating HMGB1 by antibody as Applicant appears to argue as the basis why Andersson teaches away claimed methods. Rather, the statements "the quantitative relationship between the extracellular HMGB1 pool from necrotic cells versus active secretion from macrophages, platelets, vascular endothelial cells, and other putative HMGB1 sources?" clearly and directly link Andersson's teachings regarding HMGB1 being a DNA-binding cytokine and a specific and saturable ligand for RAGE binding, and proposed further investigation of relationship between vascular endothelial cells (EC), macrophage and HMGB1 to (i) the teachings by Okamoto et al. regarding activation of RAGE signaling pathway promotes angiogenesis in cultured human skin microvascular endothelial cells (EC); and (ii) the teachings by Kirkpatrick et al. regarding the application of endothelial cell (EC) culture systems to study the effects, including pro-inflammatory cytokines, chemokines, of implanted tissue, and material factors on the regulation of the inflammatory and angiogenic response.

It is worth emphasizing that (i) the endothelial cell (EC) culture in vitro taught by combined teachings of Andersson et al., Okamoto et al., and Kirkpatrick et al. is certainly encompassed by the limitation "a tissue or part thereof" recited in claim 92 and "in vitro culture tissue" recited in claim 100 of instant application, (ii) the claimed methods do not require any specific limitation pertaining to which signaling pathway(s) HMGB1 regulates inflammatory response and promotes angiogenesis in cultured endothelial cells, and (iii) the claimed invention as a whole was clearly prima facie obvious based on combined teachings of Andersson et al., Okamoto et al., and Kirkpatrick et al. One cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references . See In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); In re Merck & Co., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).